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10/574,922	05/22/2006	Ralph Patrick Braun	092633-0104	5540

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,922	BRAUN ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *15-17,22-25 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,18-21,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Acknowledgement is made of Applicant's election of Group II, drawn to a method of eliciting a T cell response against a T cell epitope, wherein a combined administration of nucleotide sequence of interests and a protein is involved. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

As to the species election, the Office requires, identify a specific first, second, and third T cell epitope if the epitopes are different in different immunizations; and if applicable, identify a specific adjuvant. In the response, the applicant elected a single specific T cell epitope, i.e. HA antigen of the influenza virus. Accordingly, the elected species is defined as a combination of multiple doses of a single type of protein and the nucleotide encoding such without the presence of an adjuvant.

Accordingly, Claims 15-17, 22-25, 28 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse.

Claims 1-14, 18-21, 26, 27 are under current examination.

Specification

The specification contains sequence disclosures (Figures 9, 12, 18-22) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in

37 CFR 1.821(a)(1) and (a)(2) but are not present in the Sequence Listing and/or identified in the specification by sequence identifier numbers. Applicant must provide sequence identifiers, in the case that these sequences are not included in the original sequence submission, a paper copy and a computer readable copy of the Sequence Listing and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). A full response to this Office Action must include a complete response to the requirement for a Sequence Listing.

The abstract of the disclosure is objected to because it does not commence on a sheet separate from other materials of the disclosure. Correction is required. See MPEP § 608.01(b).

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/510,086, 60/526,517 and 60/567,771 fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Instant claims are directed to administer a nucleotide sequence of interest followed by a protein of interest at an interval from 21 to 365 days, whereas the priority documents disclose clusters of NOI administering without administering a protein, wherein the interval between administration was less than 21 days. The abstract of the priority documents states, "*The invention is based on the surprising finding that at least two administrations of an NOI encoding at least one EOI of a TA at intervals of from about 48 hours to about 144 hours between administrations significantly amplify the CMI response to at least one EOI of a TA*" (emphasis added). Apparently, instantly claimed invention teaches away from the priority documents. Accordingly, the priority date of instant application for the subject matter under examination has been established as the filing date of the PCT application, i.e. 10/12/2004.

Claim Objections

Claim 1 is objected to because it embraces non-elected invention. The elected invention is directed to a combination of nucleic acid and protein immunization, whereas by reciting "optionally" and "(a) a NOI…" for step (ii), the claim encompasses nucleic acid immunization only (non-elected group I). Since the applicant has elected an

invention for prosecution, the claims should be amended so that they only read on the elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is vague and indefinite because the word "or" in line 4, and the word "and" in line 5. It is unclear the relationship of the three elements and which elements are required to be co-exist, and what is the substantive difference between elements (ii) and (iii), and thus, the meets and bounds of the claims are uncertain.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 18-21, 26, 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are directed to a vaccine regimen for inducing a T cell response against a T cell epitope in a mammalian subject comprising DNA-prime and protein-boost regimen, wherein the claims are broadly encompass any antigen of interests. Although the specification contemplates the DNA prime and protein boost regimens, and the specification provides multiple examples of various plasmid vectors encoding different types of viral antigens, it does not provide a single example of protein-boost regimen. Hence, the enablement lies on the state of the art (see prior art rejections below). Although there were numerous prior art documents inducing T cell response through DNA-priming and protein-boosting, the state of the art is such there were many variations and unknown factors for different antigens, different routes of delivery, different dosing regimen, etc. For example, see teachings of *Doria-Rose et al* (Methods 2003;31:207-16). To this end, the specification fails to teach the claimed specific

regimens would apply to the genus of antigens. US patent 6,500,432 claims, for enhancing a CTL response, the polypeptide should be administered 1-10 days after the polynucleotide (see claims 1-2). It is unclear and the specification fails to teach how applicant came up with the number as recited in the claims, as opposed to the number in the claims of the '432 patent. *Rasmussen* (J Med Primatol 2002;31:40-60) reported, using DNA prime/protein boost vaccine strategy, they fail to generate a detectable or significant T cell response against HIV antigens. In view of such, the specification does not appear to provide an enabling disclosure for the full scope of the claims.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 8, 9, 11, 14, 18-20, 26, 27 are rejected under 35 U.S.C. 102(b) as being anticipated by *Billaut-Mulot et al* (Vaccine 2001;19:95-102).

Billaut-Mulot teaches a method of eliciting a T cell response against HIV viral infection in a mammalian host, the method comprises intradermal administering a pharmaceutical composition comprising a DNA plasmid vector encoding and expressing HIV Nef for three successive times at 1 week intervals, followed by a boost with recombinant Nef protein intraperioneally at 14 weeks after the first injection of the DNA (§ 2.3 page 96); Wherein the Nef coding sequence is under the control of regulatory sequence CMV promoter, BGH polyadenylation signal sequence (§ 2.1); wherein the vector is in a solution of pharmaceutical acceptable carrier. A lymphocyte response was induced as evidenced in figure 2b. Since the method was carried out to test the efficacy of the vaccine regimen, it is an assay as recited in claims 26 and 27. Accordingly, *Billaut-Mulot* anticipates instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14, 18-21, 26, 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Doria-Rose et al* (Methods 2003;31:207-16), in view of *Berglund et al*

(Vaccine 1999;17:497-507), and *Horvath et al* (Immunol Lett 1998;60:127-36), and as evidenced by *Saikh et al* (Virol 1995;214:445-52).

Instant claims are directed to a vaccine regimen comprising multiple dosing of nucleic acid vaccines in combination with protein vaccines.

Doria-Rose outlines the general state of the art pertaining to DNA vaccine strategies, including plasmid design, route of administration, and dosing regimens (see for example the abstract). *Doria-Rose* teaches the number of doses affects the immune response. A very immunogenic gene may require only a single dose, as was found for influenza HA, whereas in most cases, more than one immunization is required (§ 11, page 210). *Doria-Rose* teaches for many antigens, 1μg is all that required by a gene gun delivery (a particle acceleration device, e.g. 2nd paragraph, page 211). *Doria-Rose* teaches the timing of doses also affects the outcome of vaccination. Using recombinant HIV-1 gp120 as an example, *Doria-Rose* teaches a resting period of approximately 20 weeks between the second and third immunizations resulted in significant, often 10-fold or more increases in antibody production. *Doria-Rose* names the process as prime-boost or combination immunization, and states, "GENERALLY, THE REGIMEN BEGIN WITH ONE OR MORE DOSES OF THE FIRST VACCINE-"PRIME"-FOLLOWED BY ONE OR MORE DOSES OF THE SECOND MODALITY-"BOOST". THE FIRST MAJOR STUDY TO USE THIS APPROACH FOR SIV SHOWED STERILIZING IMMUNITY ELICITED BY PRIMING WITH A RECOMBINANT VACCINIA VIRUS THAT ENCODED SIV ENVELOPE PROTEIN AND BOOSTING WITH PURIFIED ENVELOPE PROTEIN" (paragraph bridging columns 1 & 2, page 212). *Doria-Rose* goes on to teach, "IN MANY CASES, A COMBINATION OF TWO MODALITIES ELICITS BETTER IMMUNE RESPONSES THAN EITHER VACCINE ALONE". In table I, *Doria-Rose* lists successful DNA prime-boost vaccines in animal models including

influenza vaccine using a combination of DNA plasmid and modified vaccinia Ankara. *Doria-Rose* also teaches the advantage of using antigen combinations in a DNA vector construct because different antigens are likely to be targets of antibody and cellular responses, and could cover the unique individual CTL responses, and antigen variations due to viral mutation (§ 5, page 208). *Doria-Rose* differs from instant claims in that they did not specifically mention using the DNA prime and protein boost regimen for influenza virus, or using multiple influenza antigens.

Berglund supplemented *Doria-Rose* by establishing it was well known in the art in the context of developing influenza vaccine that one could express more than one antigen of influenza virus in a vector, using multiple dosing regimen and different routes of administration. *Berglund* teaches a method of eliciting a T cell response against influenza viral infection in a mammalian host, the method comprises intranasal, intravenous, subcutaneous or intramuscular administering a pharmaceutical composition comprising a recombinant SFV vector particles encoding and expressing HA or NP, or HA & NP antigens to C57B1/6 or Balb/c mice, followed by a booster does in half of the mice at day 14 after the initial prime dose (e.g. § 3.1, page 499, fig. 3, 11, § 3.4).

Horvath supplemented *Doria-Rose* by establishing it was well known in the art that recombinant HA peptide is capable of inducing T cell responses that protect mice against influenza virus infection (e.g. the abstract and figures).

The combined teachings of *Doria-Rose* in view of *Berglund* and *Horvath* do not specifically discuss whether the CTL response is specific for a CD4+ or CD8+ epitope.

Although not relied upon, *Saikh* evidenced that influenza HA antigen comprising at least CD8+ epitope.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the DNA-prime and protein-boost strategy as taught by *Doria-Rose* in developing influenza vaccine. The ordinary skilled artisan would have been motivated to modify the claimed invention because it is likely to generate better immune response as suggested by *Doria-Rose*. Given the success as taught by *Berglund* and *Horvath*, one would have had a reasonable expectation of success combining the two. Although none of the cited references states exact timing between the DNA-priming and protein-boost for influenza virus vaccine, given the knowledge of the skilled as illustrated by *Doria-Rose*, such timing could be established through routine experimentation, and hence the limitation fall within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7:30 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
May 23, 2008